REMARKS

Claims 1, 2, 13-37, 41-49, and 56-84 are pending in this application. Claims 33, 36, 37, 42-49, and 56-84 have been withdrawn. Claims 1, 2, 13-32, 34, 35, and 41 are under examination. Claims 1 and 29 have been amended, support for which can be found throughout the specification, for example, at pages 4, 5, 6, 8-9, and 15. Claim 34 also is amended to remove its dependency on a withdrawn claim. No new matter is introduced.

Claim Objections

Regarding claim 1, the Examiner has asserted that the term "Arg-Lys-Arg-Arg-Lys-Arg (SEQ ID NO: 1)" is unclear because it is allegedly not apparent if SEQ ID NO: 1 is an example of the amino acid sequence or is the sequence identifier for the amino acid sequence. The Examiner has recommended amending the claim to read "Arg-Lys-Arg-Arg-Lys-Arg (as set forth in SEQ ID NO: 1)." Although Applicants do not necessarily concur, Applicants have amended the claim as suggested by the Examiner in an effort to expedite the examination of the pending claims.

Regarding claim 29, the Examiner has objected that it is not clear whether the claim relates to a vector or a composition comprising a vector. Applicants have amended the claim in accordance with the Examiner's suggestion.

Rejections under 35 U.S.C. § 103

Claims 1, 2, 13-25, 29-32, 34, 35, and 41 have been rejected as allegedly unpatentable over Scaria *et al.* (US 20030229036) in combination with Wolf (US 5,795,863). The claims are directed to modified Factor VII having a proteolytic cleavage site not normally present in Factor VII and introduced at a location that allows secretion of active Factor VII upon cleavage. The Examiner has asserted Scaria teaches viral vectors comprising a promoter operably linked to a nucleic acid encoding modified Factor VII. The Examiner acknowledges that Scaria does not teach or suggest Applicants' modification — Arg-Lys-Arg-Arg-Lys-Arg (as set forth in SEQ ID NO: 1). The Examiner further has asserted that Wolf teaches a coagulating protein having the same Arg-Lys-Arg-Arg-Lys-Arg modification as set forth in

the claims. According to the Examiner, the combination of the teachings in Scaria and Wolf would result in the instant claims. Applicants respectfully disagree and traverse the rejection.

The Examiner's proof of obviousness fails. The Examiner has failed to consider the teaching of the prior art as a whole. *Panduit Corp. v. Dennison Mfg. Co.*, 774 F.2d 1082, 1093-94 (Fed. Cir. 1985) ("The well established rule of law is that each prior art reference must be evaluated as an entirety, and that all of the prior art must be evaluated as a whole.") Wolf is directed toward the "*prevention* or *treatment* of thrombosis [blood clotting]" by producing an inactive Factor X. Wolf, Abstract (emphasis added); *see also* col. 3, lines 13-24; claims 3, 4, 9, 11, 14, and 16; http://www.merriam-webster.com/dictionary/thrombosis (defining thrombosis as "the formation or presence of a blood clot within a blood vessel"). In contrast, claim 1 as amended herein recites a "composition comprising a recombinant polynucleotide that encodes a modified Factor VII, said modified Factor VII comprising a proteolytic cleavage site at a location that allows secretion of active Factor VII upon cleavage, said proteolytic cleavage site having the sequence Arg-Lys-Arg-Arg-Lys-Arg (as set forth in SEQ ID NO: 1) and not normally present in Factor VII." As explained in the specification, the claimed composition promotes blood clotting by providing an active Factor VII. Instant Specification, at page 1 (in the Technical Field), at pages 1-4 (describing the state of the art in treating disorders where there is a deficiency in blood clotting); at page 4 (describing an advantage of modified clotting factors as providing active clotting factors that "obviates the need for proteolytic cleavage during the blood clotting process"). Additionally, Wolf is directed to producing an *inactive* clotting factor (Factor X) by, among other things, inserting a proteolytic cleavage site into the factor. Wolf, col. 3, lines 39-59; col. 5, lines 35-57 (describing the production of Factor X'i, which lacks the proteolytic activity necessary for blood clotting); col. 6, lines 45-50 (defining Factor X'i as a modified form of the factor that "has been inactivated at its catalytic site"). Conversely, the subject matter of the instant claims are compositions that yield an *active* Factor VII.

Instead of considering the Wolf reference as a whole, the Examiner has plucked, out of context, a reference to the modification site set forth in SEQ ID NO: 1 and combined it with another reference. When considered as a whole, the purposes of Wolf and the subject matter of the instant claims are diametrically opposed. Whereas Wolf seeks to prevent blood clotting, the instant claims are directed to compositions that promote blood clotting. Whereas

Wolf seeks to produce an inactive clotting factor, the instant claims are directed to compositions that yield an active clotting factor. By failing to consider the Wolf reference as a whole, the Examiner has failed to realize that combining the teachings or suggestions in Scaria and Wolf will not result in the instant claims - a modified Factor VII that is secreted in active form. Thus, the rejection should be withdrawn.

The Examiner has improperly combined the Scaria and Wolf references. As described above, the purposes of Wolf and the instant claims are diametrically opposed. Indeed, Wolf teaches away from compositions yielding an active clotting factor. Wolf, col. 3, lines 39-59; col. 5, lines 35-57 (describing the production of Factor X'i, which lacks the proteolytic activity necessary for blood clotting); col. 6, lines 45-50 (defining Factor X'i as a modified form of the factor that "has been inactivated at its catalytic site"). This is a classic situation where a prior art reference teaches away from the claims. *E.g. Gillette Co. v. S.C. Johnson & Sons, Inc.*, 919 F.2d 720, 724 (Fed. Cir. 1990) (the closest prior art reference "would likely discourage the art worker from attempting the substitution suggested by [the inventor/patentee].") Reading Wolf as a whole, the skilled artisan would not have thought to insert the cleavage site into Factor VII to produce an active Factor VII and to promote blood clotting, and would have, in fact, been lead in a different direction. References cannot be combined where a reference teaches away from their combination. MPEP § 2145(X)(D)(2). Thus, the rejection should be withdrawn.

Claims 1, 24, and 28 have been rejected as allegedly unpatentable over Scaria *et al.* (US 20030229036) in combination with Wolf (US 5,795,863) as applied to claims 1, 2, 13-25, 29-32, 34, 35, and 41, and further in view of Amalfitano et al. (US 6,328,958). According to the Examiner, Amalfitano teaches using an elongation factor 1-α as a heterologous promoter. As described above, the combination of Scaria and Wolf is improper and, even if proper, would not result in the subject matter of the instant claims. Accordingly, this rejection should be withdrawn.

Claims 1, 24, 26, and 27 have been rejected as allegedly unpatentable over Scaria *et al.* (US 20030229036) in combination with Wolf (US 5,795,863) as applied to claims 1, 2, 13-25, 29-32, 34, 35, and 41, and further in view of Kochanek (US 5,981,225). According to

the Examiner, Kochanek teaches a muscle creatine kinase promoter for tissue specific expression of a foreign gene. As described above, the combination of Scaria and Wolf is improper and, even if proper, would not result in the subject matter of the instant claims. Accordingly, this rejection should be withdrawn.

Claims 1, 2, 13-25, 29-32, 34, 35, and 41 have been rejected as allegedly unpatentable over Wolf (US 5,975,863) in combination with Nicolaisen (US 5,580,560) further in view of Miller et al. (US 6,924,365). The Examiner has asserted that Wolf teaches a modified coagulation protein comprising the R-K-R-R-K-R site, but does not teach Factor VII with this site. The Examiner further has asserted that Nicolaisen teaches the cDNA encoding Factor VII and the cleavage of Factor VII to Factor VIIa. The Examiner finally has asserted that Miller teaches a coagulation factor having an X-R-X-X-R cleavage site. According to the Examiner, the combination of the teachings in Wolf and Nicolaisen in view of Miller would result in the instant claims. Applicants respectfully disagree and traverse the rejection.

The Examiner's proof of obviousness fails. The Examiner has failed to consider the teaching of the prior art as a whole. *Panduit*, 774 F.2d at 1093-94. As discussed above, the purposes of Wolf and the instant claims are diametrically opposed. This is also the case for Nicolaisen. "In its broadest aspect, the present [Nicolaisen] invention provides a modified factor VII/VIIa being *stabilized against proteolytic cleavage* at certain positions in the molecule." Nicolaisen, col. 3, line 47, to col. 4, line 1. Proteolytic cleavage at many Factor VII sites leads to protein that lack clotting activity. Nicolaisen, col. 2, lines 28-48. Instead of teaching or suggesting modifying Factor VII between arginine 152 and isoleucine 153, Nicolaisen teaches to modify Factor VII at other amino acid residues, which render Factor VII *resistant* to cleavage. Nicolaisen, col. 4, lines 7-36.

Instead of considering the Nicolaisen reference as a whole, the Examiner has plucked, out of context, a reference to modifying Factor VII and combined it with another reference. When considered as a whole, the purposes of Nicolaisen and the instant claims are diametrically opposed. Whereas Nicolaisen seeks to prevent cleavage of Factor VII (Nicolaisen, col. 3, line 47, to col. 4, line 1; col. 4, lines 7-36), the purpose of the presently claimed subject matter is provision of active Factor VII by cleavage at the appropriate locus in the protein. By failing to consider the Nicolaisen reference as a whole, the Examiner has

failed to realize that combining the teachings or suggestions in Wolf and Nicolaisen will not result in the instant claims- a modified Factor VII that is susceptible to proteolytic cleavage to yield Factor VII in an active form. Thus, the rejection should be withdrawn.

The Examiner has improperly combined the Wolf and Nicolaisen references. As described above, the purposes of Wolf and Nicolaisen and the subject matter of the instant claims are diametrically opposed. This is a classic situation where a prior art reference teaches away from the claims. Reading Wolf and Nicolaisen in their entireties, the skilled artisan would not have thought to insert the cleavage site into Factor VII to promote Factor VII cleavage to yield Factor VII in an active form. References cannot be combined where a reference teaches away from their combination. MPEP § 2145(X)(D)(2). Thus, the rejection should be withdrawn.

As described above, the combination of Wolf and Nicolaisen is improper and, even if proper, would not result in the subject matter of the instant claims. Thus, the Wolf-Nicolaisen-Miller combination is improper and would not result in the instant claims. Accordingly, this rejection should be withdrawn.

Claims 1, 24, and 28, have been rejected as allegedly unpatentable over Wolf (US 5,975,863) in combination with Miller et al. (US 6,924,365) as applied to claims 1, 2, 13-25, 29, 30, 32, 34, 35, and 41 above, and further in view of Amalfitano et al. (US 6,328,958). As described above, the Wolf-Nicolaisen-Miller combination is improper and, even if proper, would not result in the subject matter of the instant claims. Accordingly, this rejection should be withdrawn.

Claims 1, 24, 26, and 27 have been rejected as allegedly unpatentable over Wolf (US 5,975,863) in combination with Nicolaisen (US 5,580,560) and Miller et al. (US 6,924,365) as applied to claims 1, 2, 13-25, 29, 30, 32, 34, 35, and 41 above, and further in view of Kochanek (US 5,981,225). As described above, the Wolf-Nicolaisen-Miller combination is improper and, even if proper, would not result in the subject matter of the instant claims. Accordingly, this rejection should be withdrawn.

Rejection for Alleged Nonstatutory Obviousness-Type Double Patenting

Claims 1, 2, 13-23, 29-32, 34, 35, and 41 have been rejected as allegedly unpatentable for nonstatutory obviousness-type double patenting over claims 1-7 of U.S. Patent No. 7,211,558 in view of Scaria et al. (US 20030229036). According to the Examiner, the 558 patent teaches a nucleic acid encoding a modified coagulation factor (Factor VIII) comprising the cleavage site set forth in SEQ ID NO: 1, but does not teach or suggest modifying Factor VII. The Examiner has asserted Scaria teaches viral vectors comprising a promoter operably linked to a nucleic acid encoding modified Factor VII. Applicants submit that this rejection is improper and inconsistent with the Examiner's requirement of a restriction/species election.

The Examiner already required that the Applicants make a restriction/species election to either modified Factor VII or modified Factor IX, to which the Applicants chose Factor VII. Office Action of Sept. 18, 2007. Now the Examiner has asserted that the pending claims to a modified Factor VII are allegedly unpatentable for nonstatutory obviousness-type double patenting over claims to modified Factor VIII in combination with Scaria's disclosure of modified Factor VII. While the composition claims have never been directed Factor VIII, it is wholely inconsistent for the Examiner to both: (a) issue a restriction/species election between different blood clotting factors (Factors VII and IX) because they are allegedly patentably distinct and (b) issue an obviousness-type double patenting rejection between different blood clotting factors (Factors VII and VIII) . Different blood clotting factors cannot *at the same time* be both *patentably distinct* and *patentably the same*. Accordingly, this rejection is improper and must be withdrawn.

Conclusion

Favorable consideration and an early notice of allowance are earnestly solicited. If the Examiner believes that a telephone conversation would further the prosecution of this case, he is invited to telephone the undersigned at his convenience.

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thrombosis

2 entries found.

thrombosis
coronary thrombosis

Main Entry: **throm·bo·sis**
Pronunciation: \thräm-ˈbō-səs, thrəm-\
Function: *noun*
Inflected Form(s): *plural* **throm·bo·ses** \-ˌsēz\
Etymology: New Latin, from Greek *thrombōsis* clotting, from *thrombousthai* to become clotted, from *thrombos* clot
Date: 1866

: the formation or presence of a blood clot within a blood vessel
— **throm·bot·ic** \-ˈbä-tik\ *adjective*